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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/540,843	03/31/2000	Barbara A. Gilchrest	0054.1088-015	2644

21005 7590 11/18/2002

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/18/2002

18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/540,843	Applicant(s) GILCHREST ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/11/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *1,3-7,9-11,13,20,23,25,51,52,57,58,63,64,69,72,81,83,86,94 and 98-109* is/are allowed.

6)☒ Claim(s) *2,14-17,19,26,29,32,75-79,82,88,89,93,95 and 97* is/are rejected.

7)☐ Claim(s) *8,71,85 and 96* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1-11,13-17, 19, 20, 23, 25, 26, 29, 32, 51,52,57,58,63,64,69,71,72,75-79,81-83,85,86,88,89 and 93-109.

DETAILED ACTION

Non-Final Rejection

Claims 1-11, 13-17, 19, 20, 23, 25, 26, 29, 32, 51-52, 57-58, 63-64, 69, 71-72, 75-79, 81-83, 85-86, 88-89, and 93-109 are pending examination.

Applicants' traversal; amendment to claims 1, 2, 4, 6-8, 13-14, 19-20, 25-26, 29, 32, 51, 57, 63, 69, 71, 75-76, 83, 85-86, 88; the addition of claims 93-109; the cancellation of claims 12, 18, 21, 22, 24, 27, 28, 30, 31, 33-50, 53-56, 59-62, 65-68, 70, 73-74, 80, 84, 87, and 90-92; amendment to the specification in paper no. 17 are acknowledged and considered by the examiner.

The objection to the specification is moot in view of the amendment to the specification.

Claim Objections

The objection to claim 1, 2, 57-58, and 69 are moot in view of the amendment to the claims.

However, in view of the amendment to the claims, the following objections apply:

Claims 8 are 71 are objected to because of the following informalities: grammatical error in claims 8 and 71. Suggest removing the comma after the term "SEQ ID NO: 5" in claim 8. Suggest removing the comma after the term "d(pT)" and adding the word "an" before the term "oligonucleotide" in claim 71.

Claim 85 is objected to under MPEP 2173.05(h), as using improper Markush group language. The claim recites, "dinucleotides, or dinucleotides dimers and combinations thereof."

The terminology ("comprising", "and", "or") in the claim is unacceptable Markush group language. The dependent claim should be recited in the conventional or alternative manner. Appropriate correction is required.

Claim 96 is objected to as being dependent upon a rejected base claim (claim 95), but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The rejection of claims 1-4, 14-16, 19, 57-58, 69, 75, 83, and 88 under double patenting is moot in view of the terminal disclaimers filed in paper no. 14.

The rejection of claim 7, 9-11, and 13 under 112 written description is moot in view of the amendment or cancellation of the claims. See page 16.

Applicants' traversal directed to the rejection of claims 1-11, 13-17, 19-23, 25-29, 31-32, 51-52, 57-58, 63-64, 69, 71-83, 85-86, 88-89 under 112 enablement is found partially persuasive because of the cancellation of claims 12, 18, 21, 22, 24, 27, 28, 30, 31, 80, 84, 87, and 90-92, and the amendment to claims 1, 7, 13, and 20. However, the traversal is not found persuasive for claims and rejection under 112 enablement for these claims remains for the reasons set forth below.

Furthermore, in view of the amended claims the following rejection under 112 written description and enablement follows:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 93 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 93 as best understood, are readable on a genus of an oligonucleotide has a nucleotide sequence homologous to the telomere repeat sequence and has melanogenic activity, wherein the genus of said oligonucleotide is not claimed in a specific biochemical or molecular structures that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of an oligonucleotide has a nucleotide sequence homologous to the telomere repeat sequence. The as-filed specification provides sufficient description of a species of a telomere DNA sequence from the 3' telomere overhang (page 7, SEQ ID NO: 5). In addition, the specification provides examples of several melanogenic oligonucleotides that either comprises of TTAGG or the dinucleotide TT (page 35).

However, the claimed genus reads on nucleotides (A, T, G, GG, AG, AGG, etc.) that must exhibit a melanogenic property and yet have any degree of similarity the telomere repeat sequence, which specific sequence of oligonucleotides do not have sufficient written support in

the as-filed specification. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of on a genus of an oligonucleotide has a nucleotide sequence homologous to the telomere repeat sequence as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of an oligonucleotide having a nucleotide sequence homologous to the telomere repeat sequence that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of an oligonucleotide that has a nucleotide sequence homologous to the telomere repeat sequence and possess melanogenic activity. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of an oligonucleotide having a nucleotide sequence homologous to the telomere repeat sequence and having melanogenic activity, wherein said oligonucleotide comprises at least one oligonucleotide that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by

describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of an oligonucleotide having a nucleotide sequence homologous to the telomere repeat sequence that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

To the extent that the applicants' traversal is applicable to the new rejection for the new claim, the traversal is not found persuasive for the following reasons: The specification does not provide sufficient description of a representative number of melanogenic oligonucleotides and the skilled artisan cannot envision the detailed structure of a genus of an oligonucleotide having a nucleotide sequence homologous to the telomere repeat sequence that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 2, 14-17, 19, 26, 29, 32, 75-79, 82, and 88, 89 remain and claims 93, 95, 97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) A method of reducing photoaging in a mammal comprising topically administering to the epidermis of the mammal an effective amount of at least one oligonucleotide wherein said oligonucleotide is approximately 2-200 bases in length and wherein the oligonucleotide comprises a phosphodiester backbone, wherein the oligonucleotide comprises a nucleotide sequence consisting of a nucleotide sequence or a portion thereof of a sequence selected from the group consisting of SEQ ID NO: 1, 2, 3, 4, 5, 6, 8, 10, and 11; 2) A method of increasing melanin production in epidermal cells, comprising topically administering to said cells an effective amount of an oligonucleotide sequence, wherein the oligonucleotide sequence selected from the group consisting of pTpT, SEQ ID NO: 1, 3, 5, and 11; 3) A method of inhibiting the proliferation of skin cells comprising topically administering to said cells an effective amount of pTpT; 4) A method of inhibiting malignant skin cells in a mammal comprising topically administering to the skin cells an effective amount of a composition comprising at least one oligonucleotide comprising a phosphodiester backbone, wherein the oligonucleotide is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO; 6, and pTpT; 5) A method of inhibiting malignant skin cells in a mammal, comprising directly administering to the cells an effective amount of DNA fragments that comprise a phosphodiester backbone and are about 2-200 nucleotides in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, dinucleotides dimers and combinations thereof, 6) A method of inhibiting malignant skin cells of a mammal, comprising topically administering to said cells an effective amount of pTpT; 7) A method of increasing melanin production in epidermal cells, wherein said method comprises topically administering to said cells an effective amount of a composition comprising at least one single-stranded

oligonucleotide, wherein the oligonucleotide has a phosphodiester backbone, and wherein the oligonucleotide comprises SEQ ID NO: 5 or is a functional fragment of SEQ ID NO: 5; and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims (e.g. a method of treating hyperproliferative disorder in a human). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a nucleotide sequence that is homologous to the telomere repeat sequence and possess melanogenic activity), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. for use in a method of increasing melanin production in epidermal cells.

The state of the art for administering oligonucleotides teaches that relatively little is known about the *in vivo* behavior of oligonucleotide (Plenat, Molecular Medicine, Vol. 1, pp. 250-275) and extrapolation from *in vitro* studies to predict pharmacokinetics and effects in a mammal are difficult and inappropriate (abstract). Furthermore, Plenat teaches that, "oligonucleotides in their natural phosphodiester form are subject to rapid degradation in the blood or intracellular fluid by exonuclease and endonucleases (page 250)." In addition, Plenat teaches that oligonucleotides are inhibited from reaching the target by side effects, which result

from interactions with cellular or extracellular proteins as well as complementarity with mRNAs for a protein other than the target (page 252).

> Furthermore, the state of the art teaches that the telomere-mimic oligomer (TTAGGG), SEQ ID NO: 11 in the instant application, was well known in the art because Page et al., (Experimental Cell Research, Vol. 252, pp. 41-49, 1999), teach, 5'-TTAGGG-3' (TAG-6) is a hexameric repeat that is added to the 3' ends of chromosomes by telomerase (abstract)."

Furthermore, the state of the art further supports the unpredictability of oligonucleotide therapy by displaying conflicting results using the specific oligomer, e.g. TTAGGG (SEQ ID NO: 11 in instant application) for inhibiting cell proliferation. Ohnuma et al. tested the cell growth inhibitory effects of telomere-mimic oligomer, using TTAGGGn, where n=1, 2, 3 or 4 on 8 human tumor cell lines (abstract). Ohnuma displays that only the 18-mer (n=3) and the 24-mer (n=4) inhibited cell growth in some of the cell lines and the 6-mer and 12-mer did not displays any cell growth inhibitory effect (page 2457, table 1). However, Page showed that, "TAG-6 can inhibit telomerase activity *in vitro* and this compound was known to have anti-proliferative effects *in vitro* and *in vivo* against a Burkitt's lymphoma cell line and xenographs in nu/nu C57 black mice (page 41)." In addition, Pages teaches that, "cytotoxicity varies among several types cell types tested with specific cells exhibiting a sensitivity not found in two other types of cell lines (page 47)." Thus, the state of the art teaches that oligonucleotide technology is characterized by a high degree of unpredictability.

Furthermore, and with respect to claims directed to DNA therapy and directed to any treatment of a mammal; the state of the art in 1998, exemplified by Anderson et al., *Nature*, Vol.

392, pp. 25-30, April 1998, displays major consideration for any DNA therapy protocol involve issues that include:

> 1) The amount of DNA constructs to be administered,
> 2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;
> 3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and
> 4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that DNA therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after DNA is delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of DNA transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any DNA therapy method to be successful (page 238, columns 1 and 2).

The disclosure provides working examples 1-16 (pages 20-41) a brief description of each example follows.

Examples 1-10 use a dinucleotide pTpT (T2). Examples 1-3 display that using T2 could inhibit different types of cancer cell lines *in vitro*. Examples 4-5 display that using T2 could inhibit different types of normal neonatal cell lines *in vitro*. Example 6 is an *in vivo* comprising topically administering T2 showing that epidermal cell proliferation could be inhibited. Example 7 displays that T2 increases p53 transcription activity in vitro. Example 8 displays that T2 enhances DNA repair via p53 in neonatal human skin cells in vitro. Example 10 displays that T2 induces IL-10 in human keratinocytes, which is likely to cooperate with TNFalpha to inhibit contact hypersensitivity in vitro.

Example 11 uses several different oligonucleotides (SEQ ID NOs: 1, 2, 3, 4, and 6, including T2) and displays that SEQ ID NOs: 1-4 stimulates melanogenesis in human melanocytes *in vitro*. However, SEQ ID NO: 6 did not stimulate melanogenesis in vitro. Example 12 uses T2 and several oligonucleotides (SEQ ID NOs: 5 and 8-12) and displays that SEQ ID NOs: 5, 8, and 10 were highly melanogenic in vitro, while the reverse complimentary sequence of SEQ ID NO: 11 (SEQ NO: 12) were less active (figure 18). However, SEQ ID NOs: 9 and 10 did not produce significant change in pigment content. Furthermore, Example 12 displays that SEQ ID NO: 1 and T2 can penetrate the skin barrier and produce *in vitro* UV-mimetic effects *in vivo*. In addition, Example 12 displays that oligonucleotide sequence plays a role in determining it melanogenic activity. In addition, Example 12 displays that 5' phosphate is required for efficient uptake.

Example 14 displays that T2 reduced UV-induced mutations *in vivo* and suggest that topical application could be used to lower the mutation rate in carcinogen-exposed skin. Example 15 tested oxidative damage by treating primary newborn fibroblast *in vitro* with T2.

The results displayed that T2 increase cell survival. Example 16 tested DNA repair capacity in newborn, young adult, and older adult fibroblast by using either T2 or SEQ ID NO: 1 containing a 5' phosphate. Pre-treatment with oligonucleotides (T2 or SEQ ID NO: 1) resulted in up regulated constitutive of UV-induced proteins (p53, p21, XPA, RPA, ERCC/PF, PCNA). In addition, pre-treatment with oligonucleotides (T2 or SEQ ID NO: 1) increased the removal of photoproducts by 30-60 percent.

Furthermore with respect to claim 2, which encompasses a method of reducing photoaging in a mammal comprising topically administering to the epidermis of the mammal an effective amount of at least one oligonucleotide wherein said oligonucleotide is approximately 2-200 bases in length and wherein the oligonucleotide comprises a phosphodiester backbone, wherein the oligonucleotide comprises a nucleotide sequence consisting of a nucleotide sequence or a portion thereof of a sequence selected from the group consisting of SEQ ID NO: 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, and 12, the as-file specification only provides sufficient guidance for one skilled in the art to use SEQ ID NO: 1, 2, 3, 4, 5, 6, 8, 11 in the claimed method. The art of record displays the unpredictability of oligonucleotide therapy and the specification fails to provide sufficient guidance how SEQ ID NO: 9 or 12 can reduce photoaging in a mammal, thus these sequences are not considered enabled because in view of the In Re Wands Factors, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from SEQ ID NO: 1, 2, 3, or 4 to SEQ ID NO: 9 or 12 for the reasons set forth above.

In addition, with respect to claims 14-17, 19, which are directed to a method of increasing melanin production in epidermal cells comprising contacting said cells with an effective amount of at least one oligonucleotide, wherein the oligonucleotide comprises at least one sequence

selected from the group consisting of pTpT, SEQ ID NO: 1, 2, 3, 4, 5, 11, and 12. The disclosure provides working examples displaying that several oligonucleotide sequences (SEQ ID NOs: 1, 3, 5, 6, and 11) stimulate melanogenesis in cells *in vitro* (Examples 11 and 12). Thus, the as-filed specification provides sufficient guidance to display that a DNA sequence from the 3' telomere repeat selected from SEQ ID NOs: 5 or portion thereof (SEQ ID NO: 11) can stimulate pigmentation in cells *in vitro*. In addition, the specification provides sufficient guidance showing that SEQ ID NO: 7 (also named SEQ ID NO: 3) and 5 stimulate melanin production in epidermal cells. Furthermore, the unpredictability of using oligonucleotides provided by the art of record is confirmed by the working examples showing **neither SEQ ID NO: 9 or 12 did not produce significant change in pigment content**. In addition, the chemical structure of SEQ ID NOs: 9 and 12 are distinct compared to either SEQ ID NOs: 5 or 7. **The specification provides sufficient guidance displaying that either SEQ ID NOs: 5, 3, and portion thereof (SEQ ID NO: 11) can stimulate melanin production in epithelial cells and not for SEQ ID NO: 9 or 12.**

Furthermore, the art of record teaches that at the time the application was filed *in vivo* administration of oligonucleotides by any route of administration other than direct administration to the cells or topically administering to skin cells so as to produce a therapeutically useful effect was considered by those skilled in the art to be an undeveloped and unpredictable method of treatment, due to the difficulties in delivering therapeutically effective amounts of any given oligo to the correct cellular component of the target cells *in vivo*. For treatment of targeted cancer cells *in vivo*, the chemical structure of the oligos (sequence residues) the length of the oligo, the binding site in the target location in the cell, the chemical composition of the carrier

employed to promote cellular uptake, the type of cell targeted, the location of the cell, and the animal being treated, are critical parameters which determine, whether or not the oligonucleotide therapy as claimed will be successful. Hoke et al. (US Patent No. 5,585,479), provide reasons to support the lack of reasonably correlation between the primary structure of an oligonucleotide to and its activity *in vivo*. More specifically, Hoke discloses that moving the target just one or two bases can greatly reduce, or even eliminate, oligonucleotide activity. Hoke states that, "based upon the above discussions of oligonucleotide activity for oligos that are similar in length and complementary to the same nucleotides, there are no rational explanations or rules that would predict active sequences (column 16, lines 50-54)."

Furthermore, the art of record encompassing the obstacles of nucleic acid therapy by using any naked nucleic acid including oligonucleotides as therapeutic agents, Stull et al., (Pharmaceutical Research, Vol. 12, pg. 476, 1995), which is a review article, discloses that "nucleic acid drugs must overcome several formidable obstacles before they can be widely used as therapeutics", furthermore, "these obstacles require improving the stability of polynucleotides in biological systems, and efficacy of the drug without reducing its selectively may adversely affect the affinity or activity of the reagent."

Furthermore, the concerns set forth above are further confirmed by the review article by Branch (TIBS, Vol. 23, pp. 45-50, 1998), Branch states that:

> "Non-antisense molecule effects are not the only impediments to rational antisense drug design. The internal structure of target RNAs and their association with cellular proteins create physical barriers' (page 45);
> "The challenge is to identify antisense molecules that are complementary to vulnerable sites in target RNAs. This is hard to do. RNAs are complex molecules with intricate structures" (page 49);
> "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49); and

> "It is not clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo* techniques, straightforward new screening techniques need to be developed for use in cells" (page 49)

Thus, one skilled in the art attempting to practice the claimed invention would first look to the as-filed specification for guidance as to which of the DNA fragments to use as therapeutic nucleic acids for treating any cell including epithelial cells. The as-filed specification uses epithelial cells *in vitro* or topically administering fragments to skin cells. However, the art of record indicates that determination of DNA sequences effective for use in any therapeutic method remains unpredictable. Furthermore, determining an effective fragment and transferring the fragment to an adequate number of cells *in vivo* and getting specific binding between the fragment and the target location in an amount sufficient to produce a therapeutic effect in any mammal remain unpredictable at the time the invention was made (See Stull et al.; Branch; Hoke et al.; Anderson, Verma; Ohnuma, Plenat, and Page). The art of record indicated that several obstacles must be overcome before DNA fragments are employed in any therapeutic method in any mammal including humans. In addition, the as-filed specification uses epithelial cells *in vitro* or topically administering fragments to skin cells and it would take one skilled in the art an undue amount of experimentation to reasonably correlate from skin cells to any other cells *in vivo* because each type of cell functions as an individual entity and possesses different cellular mechanisms responding to a variety of different environmental cues, which can not be duplicated *in vitro*. Therefore, the as-filed specification fails to address any of these issues, which would therefore lead one skilled in the art to believe that *in vivo* administration of any of the disclosed DNA fragments for use in any cells other than skin cells so as to generate a therapeutic effect would be unpredictable.

Furthermore, with respect to claims 88, 89, and 95, which are directed to a method of treating malignant cells of a mammal, comprising administering to said cells an effective amount of DNA fragments. The specification displays an *in vitro* assay that shows that T2 inhibits cell growth rate in various human carcinoma cells (Examples 1, 2, 3). The disclosure states that, "the response of cancerous cells to T2 is identical to that observed after UV irradiation of these cells and is similar to the response to various antimetabolites that are clinically effective in the treatment of hyperproliferative skin disorders (page 22)." Furthermore in view of the specification, which states that, "any epithelial cell is suitable for the method of the claimed invention (page 8)." As stated above in view of the art of record, the as-filed specification is only enabled for treating skin cells by topically to said skin cells or directly administering DNA fragments selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof to epithelial cells because other routes of administration such as orally, intravenously, instillation into the bladder, etc. would expose the fragments to the acidity of the stomach, the host's immune response, the blood stream, which would result in the degradation of the fragments and the fragments would not reach the target cell at a therapeutic level. Furthermore, the breadth of the term "malignant cell" encompasses any cell (lung, liver, muscle, heart, kidney, brain, etc.) in a mammal and the specification only provides sufficient guidance for how to inhibit malignant skin cells. Each cell possesses different biological functions and structure compared to a skin cell and the properties of a skin cell does not reasonably correlate to any other cell in a mammal. The art of record is absent of any DNA fragment that can be used in a method of inhibiting any malignant cell in a mammal and the art of record teaches the unpredictability of oligonucleotide

therapy. Therefore, the claimed invention is only enabled for a method of inhibiting malignant skin cells of a mammal, comprising topically administering to malignant cells that are skin cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof.

In addition, claims 26, 29, and 32 are directed to a method of inhibiting proliferation of epithelial cells using pTpT are directed to using any route of administration. The as-filed specification displays *in vitro* assays showing inhibition of normal human neonatal keratinocyte or fibroblast cells (Examples 4 and 5). In addition, the guinea pigs received topical applications of T2 for three days and on the fourth day punch biopsies were taken and the results displayed inhibition of the cells isolated from the pigs (Example 6). Claims 26, 29 and 32 of the instant application require administrating DNA to said cells. The as-filed specification does not enable one skilled in the art to contact a cell or administer to malignant cells the DNA fragments as claimed, except when administered topically to the epidermis as contemplated by claim 85. The state of the art for oligonucleotide therapy is considered unpredictable as set forth above. The disclosure demonstrates *in vitro* data, however, the disclosure does not teach one skilled in the art how to use a DNA fragments in any route of administration other than topically. For example, any route of administration such as orally, intravenously, instillation into the bladder, etc. would expose the fragments to the acidity of the stomach, the host's immune response, the blood stream, which would result in the degradation of the fragments and the fragments would not reach the target cell at a therapeutic level. Thus, in view of the as-filed specification and the art

of record, claims 26, 29 and 32 are only enabled for a method of inhibiting proliferation of malignant skin cells comprising topically administering an effective amount of pTpT.

Furthermore, with respect to method in claim 75 and claims independent therefrom, the methods are only enabled for direct administration to epithelial skin cells for the art of record set forth above (see Stull et al.; Branch; Hoke et al.; Anderson, Verma; Ohnuma, Plenat, or Page) concerning route of administration and using a phosphodiester backbone.

Furthermore, with respect to the method of treating a hyperproliferative disorder in a human in claim 82, the claim is not enabled in view of the In re Wands Factors. More specifically, the specification does not define the term "treating" and in view of the breadth of phrase "treating a hyperproliferative disorder in a human", the term encompasses curing or complete regression of said disorder in a human and the as-filed specification only provides sufficient guidance for one skilled in the art to treat a hyperproliferative disorder in a mammal using the claimed DNA fragments taught in the specification. The state of the art teaches "the spontaneous behaviour of human tumors is somewhat different from that of malignant cells in vitro, and from the of experimental tumors in animal models (Gomez-Navarro et al, European Journal of Cancer, Vol. 35, 1999, page 868) and development of better animal models is required." Furthermore, the state of the art at the time the application was filed was absent about treating any hyperproliferative disorder in a human. Thus, in view of the art of record (for example see Stull et al.; Branch; Hoke et al.; Anderson, Verma; Ohnuma, Plenat, or Page) and the lack of guidance provided by the as-filed specification for how one skilled in the art can reasonably correlate treating a hyperproliferative disorder in a mammal (e.g. mouse) to treating a

hyperproliferative disorder in a human, it would take one skilled in the art an undue amount of experimentation to use any oligonucleotide in the claimed therapeutic method.

Furthermore, with respect to claim 93, the as-filed specification is only enabled for using an oligonucleotide sequence that either consists of the telomere repeat sequence (SEQ ID NO: 5) or is a functional fragment thereof. The breadth of the phrase "homologous to the telomere repeat sequence" reads on sequences (A, T, G, AGG, TA, GG, etc.) that would not increase melanin production in epidermal cells. The claimed genus encompasses species that are not considered enabled in view of the art of record or the as-file specification. Thus, it would require one skilled in the art an undue amount of experimentation to determine if a representative number of species of oligonucleotides that are homologous to the telomere overhang would be enabled for one skilled in the art to use them in a method to increase melanin production in epidermal cells of a mammal.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed DNA fragments generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any oligonucleotide therapy method as contemplated by the claims, particularly given the unpredictability of oligonucleotide therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the for 1-7 listed above. Given that oligonucleotide therapy wherein any DNA fragment is employed to treat a disease or a medical condition in any mammal was unpredictable at the

time the invention was made, and given the lack of sufficient guidance as to a oligonucleotide therapy effect produced by any DNA fragment cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of oligonucleotide therapy. Thus, oligonucleotide therapy was considered unpredictable at the time the invention was made.

Applicants traverse the rejection under 112 enablement for the following reasons: Applicants demonstrated that oligonucleotides can be administered to guinea pigs with a measurable biological effect on the skin. From these demonstration, it can be concluded that adjustments of dosages and regimens of administration of the oligonucleotides should be straightforward; the methods of the claims do not require the use of oligonucleotides known to be part of a coding region or a non-coding region of a gene; It cannot be assumed that the difficulties found in antisense methods will apply to the methods of the claims; The Hogrefe review shows that in clinical trials, several types of malignancies have been treated by oligonucleotides administered by known routes other than topical administration and that these in vivo routes of administration have been effective. See pages 16-20.

Applicant's traversal is acknowledged and to the extent that the traversal is applicable to the rejections under 112 enablement, it is not found persuasive for the following reasons: in view of the In Re Wands Factors, the as-filed specification and the applicants' traversal do not provide sufficient guidance and/or factual evidence for one skilled in the art to reasonably extrapolate from direct administration (topical) to skin cells using the claimed oligonucleotides having a phosphodiester backbone to using any route of administration to any cell with said oligonucleotides without an undue amount of experimentation. Furthermore, the as-filed

specification fails to provide sufficient and/or factual evidence for one skilled in the art to use the full scope of claim 2 or the full scope of claim 14 because of the art of record for the unpredictability of oligonucleotide therapy comprising using any sequence set forth in the above claims.

It is acknowledged that Anderson and Verma are directed to the art of gene therapy using a DNA coding sequence, however DNA oligonucleotide sequences and DNA coding sequences share the same problems with *in vivo* administration because both are DNA sequences and share the same chemical properties. Thus, one skilled in the art would understand that oligonucleotide therapy shares the same problems with gene therapy.

In addition, Exhibit A displays that most of the antisense compounds progressing through clinical trials at this time are phosphorothioates (See Table 1). The applicants' traversal states, "it cannot be assumed that the difficulties found in antisense oligonucleotide methods will apply to the methods of the claims." Thus, it is not apparent how the problems of anti-sense therapy cited in the 112 enablement rejection cannot be applied to the claimed invention because the applicants' traversal cites an antisense paper for support for any route of delivery for oligonucleotides of the claimed invention, while stating that problems with antisense would not apply to the methods of the claims. Furthermore, the reason for using phosphorothioate backbone instead of a phosphodiester backbone for any route of administration is further supported by problems acknowledged by Plenat, who teaches that, "oligonucleotides in their natural phosphodiester form are subject to rapid degradation in the blood or intracellular fluid by exonuclease and endonucleases" (page 250). In addition, the as-filed specification only displays direct administration to an ear or skin of mice. Furthermore, it is not apparent to one skilled in

the art how to target the skin of a mammal using any route of administration (oral, inhalation, rectal, etc.) other than direct (topical) administration. Thus, in view of the art of record and the lack of guidance provided by the specification, it would take one skilled in the art would an undue amount of experimentation to reasonably extrapolate from using a direct administration to any route of administration especially with the problems associated with why clinical trials are using phosphorothioate backbone instead of phosphodiester backbone for use in any route of administration.

The rejection of claims 4 and 13 under 112 second paragraph are moot in view of the amendment to the claims. See pages 20-21.

However, in view of the amended claims, a new rejection under 112 second paragraph follows:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 7 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 14 recite the limitation "said cells". There is insufficient antecedent basis for this limitation in the claim.

Applicants' traversal is not found persuasive because it is not applicable to the new rejection set forth above under 112 second paragraph.

The rejections for claims 51-52 under 102(e) are moot in view of the amendment to the base claim. See page 21.

The rejection for claim 85 under 102(e) is moot in view of the amendment to the claim. See pages 21-22.

The rejection for claim 88 under 102(e) is moot in view of the amendment to the claim. See page 22.

Claims 1, 3-11, 13, 20, 23, 25, 51-52, 57-58, 63, 64, 69, 71, 72, 81, 85, 86, 94, 96, 98-109 are in condition for allowance because the claims are free of the prior art.

No other claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
11/15/02

DAVE T. NGUYEN
PRIMARY EXAMINER